Elevated miR-499 levels blunt the cardiac stress response.

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Public Summary:
The heart reacts to stress through a variety of genetic responses. RNA is normally used by cells to make proteins. Tiny fragments of RNA, called microRNA, regulate this process. This unique property allows microRNAs to regulate a myriad of cellular events. We studied a particular microRNA called miR-499, which is found in heart and skeletal muscle. In experiments with transgenic mice, we found that elevated levels of miR-499 caused heart cells to enlarge, resulting in cardiac dysfunction. Our findings indicate that miR-499 may cause the heart to adjust its reaction to stress by regulating genes that are activated rapidly in response to cellular stimuli.

Scientific Abstract:
BACKGROUND: The heart responds to myriad stresses by well-described transcriptional responses that involve long-term changes in gene expression as well as more immediate, transient adaptations. MicroRNAs quantitatively regulate mRNAs and thus may affect the cardiac transcriptional output and cardiac function. Here we investigate miR-499, a microRNA embedded within a ventricular-specific myosin heavy chain gene, which is expressed in heart and skeletal muscle. METHODOLOGY/PRINCIPAL FINDINGS: We assessed miR-499 expression in human tissue to confirm its potential relevance to human cardiac gene regulation. Using a transgenic mouse model, we found that elevated miR-499 levels caused cellular hypertrophy and cardiac dysfunction in a dose-dependent manner. Global gene expression profiling revealed altered levels of the immediate early stress response genes (Egr1, Egr2 and Fos), ss-myosin heavy chain (Myh7), and skeletal muscle actin (Acta1). We verified the effect of miR-499 on the immediate early response genes by miR-499 gain- and loss-of-function in vitro. Consistent with a role for miR-499 in blunting the response to cardiac stress, asymptomatic miR-499-expressing mice had an impaired response to pressure overload and accentuated cardiac dysfunction. CONCLUSIONS: Elevated miR-499 levels affect cardiac gene expression and predispose to cardiac stress-induced dysfunction. miR-499 may titrate the cardiac response to stress in part by regulating the immediate early gene response.